PATENT SPECIFICATION

NO DRAWINGS

1,179,060

Date of Application (No. 32834/68) and filing Complete Specification: 10 July, 1968.

Application made in United States of America (No. 656,669) on 28 July, 1967.

Complete Specification Published: 28 Jan., 1970.

Index at acceptance:—C2 A(1C2A, 1C2C, 2C1); C2 C(3A12A4C, 3A12B7, 3A12C5, 3A14A2A, 3A14A7B, 3A14B3A, 3A14B3B, 3A14B8A, 3A14B8C, 22Y, 22X, 227, 30Y, 32Y, 321, 366, 367, 45Y, 45X, 450, 490, 620, 628, 660, 668, 17X—178—183, LR)

International Classification:—C 07 d 99/16

COMPLETE SPECIFICATION

Penicillanic Acids

PATENTS ACT 1949

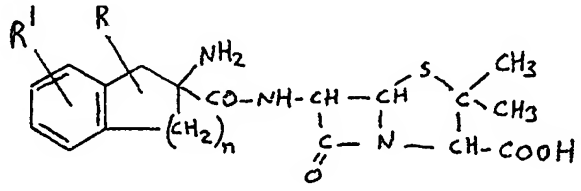
SPECIFICATION NO. 1,179,060

The following corrections were allowed under Section 76 on 25 February 1972:-

Page 6, line 4, *delete* 2- aminoindane *insert* 2-carbobenzyloxyaminoindane

THE PATENT OFFICE
24 March 1972

R 9059/13



I

and salts thereof wherein R^1 and R^2 are the same or different and each is hydrogen, lower alkyl, lower alkoxy, aryl (eg. phenyl) or aryloxy (eg. phenoxy); n is equal to 1 or 2, and the term "lower" means that the radical contains up to 6 carbon atoms.

The novel compounds of the above general formula may be prepared using methods known *per se* for preparing penicillins. In general, the compounds preferably are prepared by reacting a suitable 4-substituted-2, 5-oxazolidinedione (also known as an N-carboxy amino acid anhydride or NCA) with 6-amino penicillanic acid (6—APA). Preferably, a solution of 6—APA and triethylamine is first prepared which is slightly acid (e.g. pH 6), the selected N-carboxy anhydride is then added, and the reaction mixture stirred at room temperature. The novel compounds of the above general formula, resulting from the reaction between 6—APA and the N-carboxy amino acid anhydride may then be recovered by conventional procedures such as filtration, concentration, water extraction and precipitation from organic solvents, such indicated. If desired, salts can be prepared from the penicillins in known manner.

The N-carboxy anhydrides used for the preparation of the penicillins of general formula I are compounds of general formula VI given below and can be prepared according to the following reaction scheme

[F

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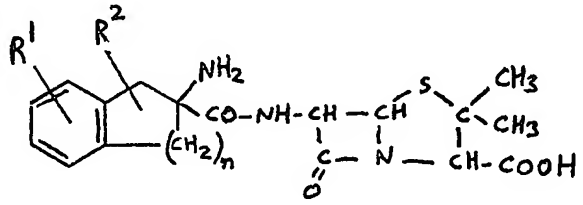
COMPLETE SPECIFICATION

Penicillanic Acids

We, AMERICAN HOME PRODUCTS CORPORATION, a corporation organised and existing under the laws of the State of Delaware, United States of America, and having a place of business at 685 Third Avenue, New York City 17, New York, United States of America, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to new synthetic penicillins having potent activity against gram-negative and particularly against gram-positive micro-organisms, to a process for the preparation thereof and to pharmaceutical compositions containing the penicillins.

The new synthetic penicillins of the present invention are compounds of the following structural formula:



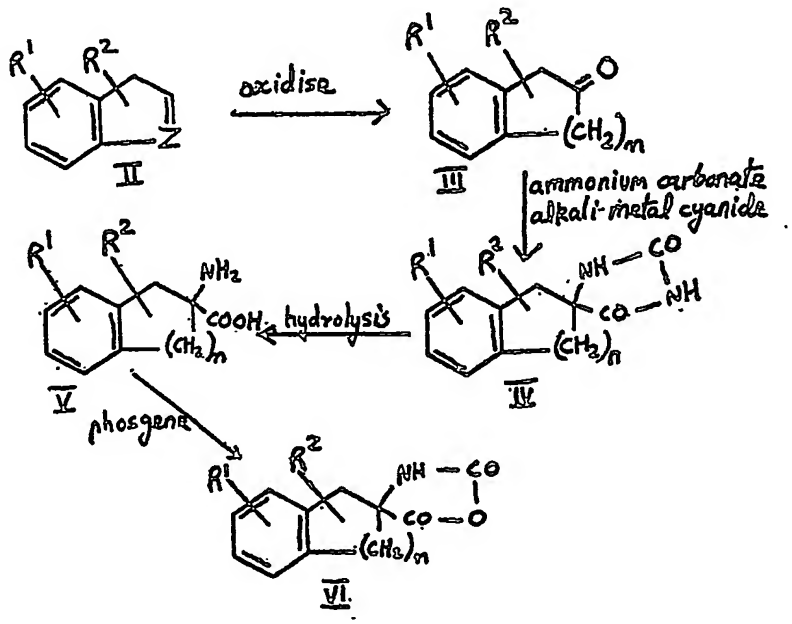
I

and salts thereof wherein R^1 and R^2 are the same or different and each is hydrogen, lower alkyl, lower alkoxy, aryl (eg. phenyl) or aryloxy (eg. phenoxy); n is equal to 1 or 2, and the term "lower" means that the radical contains up to 6 carbon atoms.

The novel compounds of the above general formula may be prepared using methods known *per se* for preparing penicillins. In general, the compounds preferably are prepared by reacting a suitable 4-substituted-2, 5-oxazolidinedione (also known as an N-carboxy amino acid anhydride or NCA) with 6-amino penicillanic acid (6—APA). Preferably, a solution of 6—APA and triethylamine is first prepared which is slightly acid (e.g. pH 6), the selected N-carboxy anhydride is then added, and the reaction mixture stirred at room temperature. The novel compounds of the above general formula, resulting from the reaction between 6—APA and the N-carboxy amino acid anhydride may then be recovered by conventional procedures such as filtration, concentration, water extraction and precipitation from organic solvents, such indicated. If desired, salts can be prepared from the penicillins in known manner.

The N-carboxy anhydrides used for the preparation of the penicillins of general formula I are compounds of general formula VI given below and can be prepared according to the following reaction scheme

[F



wherein R^1, R^2 and n, each has the same meaning defined respect to Formula I above, and Z is:

$$—CH= \text{ or } —CH_2—CH<$$

Thus, an indene (Z is —CH= in formula II) or 1, 2, 3, 4-tetrahydronaphthalene (Z is $—CH_2—CH=$ in formula II) which substance is often known as tetralin, can be oxidised following the method of Rose, Dorfman and Linfield [Journal of Organic Chemistry, *29*, 1793, (1964)] to the corresponding 2-indanone of 2-tetralone of general formula III. The α-indanone or tetralone may be heat-reacted with ammonium carbonate and an alkali metal cyanide (eg. potassium cyanide) in an inert organic solvent. The reaction mixture may be cooled, poured into water and acidified to pH 2 with concentrated hydrochloric acid, for example. The crude product may then be dissolved in diluted sodium hydroxide, filtered, and the filtrate re-acidified and filtered to give the corresponding 2-indanone or 2-tetralone hydantoin of general formula IV. Ring splitting hydrolysis of this hydantoin, for example by refluxing the hydantoin of general formula IV can then be carried out in the presence of an alkali metal or alkaline earth metal hydroxide (e.g. potassium or barium hydroxide) under an inert atmosphere, e.g. nitrogen, the pH adjusted to 2 with for example, concentrated hydrochloride acid, and the mixture filtered. The filtrate may be adjusted to pH 6 e.g. by addition of concentrated ammonium hydroxide to cause the amino carboxylic acid of general formula V to crystallize from solution.

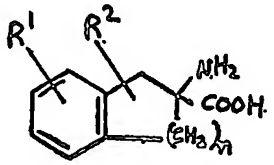
The corresponding N-carboxyanhydrides of formula VI may be prepared by reacting an amino acid of formula V with phosgene under anhydrous conditions. After addition of a low boiling solvent medium, such as an ether-ethylacetate system, reduction of the temperature of the resulting solution results in slow crystallization of the N.C.A. therefrom.

The N-carboxyanhydrides of formula VI may also be prepared by other known methods, such as those referred to or described in U.S.A. Patent Specification No. 3,194,802.

Several of the starting compounds which may be employed in the procedure referred to above for making the hydantoins of formula (I) are known compounds which are readily available from commercial sources. Others, which are not commercially available, can easily be prepared in accordance with standard organic procedures well known to those skilled in the art.

Although the above-described method is generally preferred for preparing the compounds of the present invention, other suitable methods known in the art for

preparing penicillin derivatives may be used. One such method is the coupling of 6-aminopenicillanic acid with an acid of the general formula:

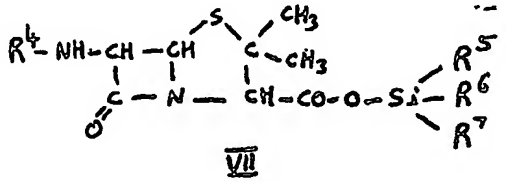


IV

or a salt thereof (where R^1, R^2 and n have the meanings defined above and in which acid or salt the amino group is protected) and thereafter removing the protecting group under sufficiently mild conditions to avoid destruction of the penicillin nucleus. In order to carry out such a coupling reaction, the acid of the above general formula preferably is reacted as the mixed anhydride obtained by reaction of the acid of the above general formula with an ester of chlorocarbonic acid, for example ethyl chlorocarbonate. Alternatively, the acid can be converted to the acid halide and this halide used for the coupling.

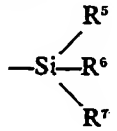
The protecting group on the said acid or derivative thereof can be any of the standard protecting groups known in this art. These include the trityl group and groups of the general formula R^3 OCO where R^3 is an allyl, benzyl, substituted benzyl, phenyl or substituted phenyl group. Such groups can be removed after the reaction by hydrogenation, preferably using a catalyst such as palladium or other suitable noble metal on a support. The hydrogenation generally is carried out at a pH of from 5 to 9 in solution in a solvent, for example water or any other appropriate non-reducible solvent, such as ethyl alcohol or dioxane or mixtures thereof with water.

Another method which can be used for preparing the compounds of the present invention is the silyl route. In this instance, a silyl derivative of 6-aminopenicillanic acid of the general formula



VII

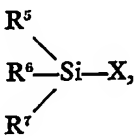
(where R^4 is a hydrogen atom or the radical



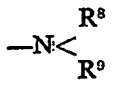
and R^5, R^6 and R^7 are the same or different and each is an alkyl, cycloalkyl, aryl, or aralkyl group) or a solution comprising such a silyl derivative, is reacted with an acid of general formula V given above or with a reactive derivative thereof (in which R^1, R^2, n have the meanings defined above but in which acid or reactive derivative thereof the amino group is protected) and thereafter removing the silyl group(s) by hydrolysis or alcoholysis. The amino group in this silyl reactant generally is protected by protonating it, reacting the compound in the form of an N-carboxyanhydride or condensing it with an aromatic hydroxy-aldehyde to give a Schiff's base. The reaction of the silyl derivative with the acid of general formula V preferably is carried out in the presence of a base, for instance a tertiary amine for example triethylamine. Alternatively, other proton accepters can be used and one example of these is excess of the silyl derivative. Reacting derivatives of the compound of formula V include functional esters, carboxylic acid halides (such as the chloride or bromide), acid anhydrides or mixed anhydrides with other carboxylic, sulphonic or inorganic acids, as well as derivatives obtained from the carboxlic acid and a carbodiimide or N,NZ-carbonyldiimidazole. Standard reaction temperatures and conditions for the silyl reaction should be used, and the presence of water and alcohols should be avoided

until after the desired final product has been obtained. Ketones and hydrocarbons (for example tetrahydrofuran or benzene) are recommended as solvents. Furthermore, the reaction can be carried out under an atmosphere of nitrogen if desired. The hydrolysis or alcoholysis of the products obtained may be effected by adding water, an aliphotic alcohol or a phenol to the reaction mixture.

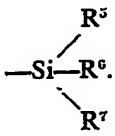
Silyl derivatives of general formula VII are known in the art and can be prepared by reacting 6-aminopenicillanic acid or a salt thereof with a compound of the general formula



where R^5, R^6 and R^7 have the meanings defined above and X is a halogen atom, the radical



(where R^8 and R^9 are the same or different and represent hydrogen atoms or alkyl radicals containing one to six carbon atoms) or the group



Generally an organic amine is present during the preparation of these silyl derivatives. The silyl derivatives preferably are prepared in solution in an organic solvent such as benzene, dioxane, or dimethylformamide and, afterstirring for several hours, the desired solution is obtained. This solution can be used directly to prepare the penicillins or, alternatively, the solvent can be evaporated *in vacuo* and the silyl compound crystallised out.

The above general methods for preparing penicillins are well known in the art and reference may be had for example to U.K. specification No. 873049, 959853, 964449 and 1,008,468.

The new penicillin compounds of general formula I, and their salts show desirable broad spectrum antibacterial activity and are useful as therapeutic agents for poultry and mammals in the treatment of infectious diseases caused by gram-positive and gram-negative bacteria, and of surprisingly greater activity with respect to the former, and particularly strains of *Streptococcus* and *Staphylococcus*, by either parenteral or oral administration. They also have use as nutritional supplements in animal feed.

As will be understood by those skilled in the art, the penicillin compounds of general formula 1 may be utilised in their acid form or in the form of the therapeutically-active salts thereof, e.g., the sodium or potassium salts, or hydrochloride, sulphate or fumarate, or in the form of the pharmaceutically-acceptable acid addition salts prepared by the reaction of the penicillin compounds with an amine or diamine base, *e.g.*, procaine or various N-N′-disubstituted alkylene diamines, such as N,N′-dibenzylethylene-diamine.

The invention also provides a pharmaceutical composition comprising a compound of general Formula I, or a non-toxic salt thereof, and a pharmaceutically acceptable carrier. The carrier may be solid, liquid or a mixture thereof and any suitable carrier known in the art can be used. The composition may be in the form of, for example, a solution, suspension, tablet or capsule utilising conventional solvents, suspensoids or excipients.

The following non-limiting examples illustrate the invention:

EXAMPLE 1

6-(Indan-2-amino-2-carboxamido)penicillanic acid

A. Preparation of 2-indanone.

325 ml. of 99% formic acid, 43 ml. of water, and 70 ml. of 30% hydrogen peroxide were mixed and warmed to 35°C over fifteen minutes. Freshly distilled

indene (58.1 gms) was added over 2 hours while maintaining a temperature of 34—36°C with a cool water bath. The mixture was stirred an additional hour at 34—36°C and then overnight at room temperature.

10.6 gms. of the heptahydrate of ferrous sulphate were added in 53 ml. of water to remove the active oxygen compounds and the solution was concentrated to 170 ml. *in vacuo*. A solution of 140 ml. of concentrated H_2SO_4 in 860 ml. of water was added and 200 ml. of distillate was steam distilled. The distillate was extracted with 3 x 100 ml. of methylene chloride. The extracts were combined and washed with 500 ml. of water, dried over Na_2SO_4 filtered, and evaporated to an oil which crystallised; m.p. 57—59°C.67%.

B. Preparation of 2-indanone hydantoin

2-Indanone, 22.5 gms. (0.17 moles), ammonium carbonate monohydrate 48.5 gms. (0.425 moles), and potassium cyanate 16.3 gms. (0.25 moles) were mixed in 210 ml of formamide and heated in a pressure bomb at 100°C overnight. The cooled reaction was diluted with 600 ml. of water and acidified with concentrated HCl to pH 2 with good ventilation. The precipitate was filtered, washed with water and dried. mp 255—7°C Yield: 46.5 gms. wet. The material was purified by dissolving in 5% aqueous NaOH, extracting with ether, and acidifying, m.p. 260—262°C.

C. Preparation of 2-aminoindane-2-carboxylic acid.

2-Indanone hydantoin 55.75 gms. (0.274 moles), barium hydroxide octahydrate 215 gms. (0.685 moles) and 300 ml. of water were heated in a bomb at 200°C for 20 hours. The pressure reached 250 psi. The hydrolysis mixture was acidified with concentrated HCl to pH2, heated to boiling, treated with Darco (Registered Trade Mark) G—60 and filtered. 38 ml. of concentrated H_2SO_4, was added to the filtrate with stirring and the slurry was heated and filtered. The Ba SO_4 precipitate was washed with hot water and the combined filtrates were evaporated to dryness. The residue was dissolved in 100 ml of water and adjusted to pH 4.5 with aqueous NaOH and chilled. The product was dried. A second crop was obtained by concentrating the mother liquer.

Yield:	1st Crop.	12.2 gms.	m.p. 309—311°C
	2nd Crop	3.8 gms.	m.p. 291—293°C
Total		16.0 gms	33%

D. Preparation of 2-aminoindane-2-carboxylic acid NCA.

2-Aminoindane-2-carboxylic acid 11.9 gms. (0.068 moles) was stirred in 250ml. of anhydrous dioxane, and phosgene was introduced as the temperature was raised to 90°C. The temperature was maintained at 90°C for 2 hours as phosgene was bubbled into the solution. The phosgene was stopped and the reaction was flushed with dry nitrogen at room temperature overnight. The solvent was removed *in vacuo* and the residue was triturated with hexane, and filtered. Yield: 12.0 gms., 89% m.p. 123—125°C. This was recrystallized from ethyl acetate-hexane. Yield: 8 gms., 59%, m.p. 156—157°C.

E 6-(Indan-2-amino-2-carboxamido)penicillanic acid.

Five grams of N-carboxy-indan-2-amino-2-carboxylic acid anhydride was added with stirring to a solution containing 5.6 gms. of 6—APA in 100 ml. of water adjusted to pH 6.0 with triethylamine. The reaction mixture was stirred overnight at room temperature, then adjusted to pH 5.0 and the insoluble product collected. After drying in vacuo at room temperature, it weighed 6.6 g.

Calcd. for $C_{18}H_{21}N_3O_4S.2H_2O$:	C, 52.5; H, 6.1; N, 10.2
Found:	C, 52.6; H, 6.0, N, 10.1

EXAMPLE 2

Following the procedures of Example 1, A—E, the appropriate 2-indanones, or 1,2,3,4-tetrahydro-naphthanones, and the corresponding hydantoins, carboxylic acids, and ultimate N-carboxy amino acid anhydrides thereof, were prepared, and the latter, as given in Table A below, were respectively reacted with 6—APA to obtain the respective penicillin products also given in the Table.

TABLE A

N-Carboxy Amino Anhydride of	*Penicillanic Acid Product formed*
2-Amino-1,2,3,4-tetrahydro-6-methoxy-2-naphthoic acid	6-(2-Amino-1,2,3,4-tetrahydro-6-methoxy-2-naphthamido penicillanic acid
2-Amino-1,2,3,4-tetrahydro-7-ethoxy-2-naphthoic acid	6-(2-Amino-1,2,3,4-tetrahydro-7-ethoxy-2-naphthamido)penicillanic acid
2-Amino-1,2,3,4-tetrahydro-3,6-dimethyl-2-naphthoic acid	6-(2-Amino-1,2,3,4-tetrahydro-3,6-dimethyl-2-naphthamido)penicillanic acid
2-Amino-4-phenyl-2-indancarboxylic acid	6-(Indan-2-amino-4-phenyl-2-carboxamido)penicillanic acid
2-Amino-3-phenoxy-2-indancarboxylic acid	6-(Indan-2-amino-3-phenoxy-2-carboxamido)penicillanic acid
2-Amino-4-butyl-2-indancarboxylic acid	6-(Indan-2-Amino-4-butyl-2-carboxamido)penicillanic acid

EXAMPLE 3

Ethyl chlorocarbonate was added dropwise to an ice-cooled stirred solution of 2-aminoindane-2-carboxylic acid in anhydrous dioxane and containing triethylamine, whereby the mixed anhydride was formed. The resulting reaction mixture was treated slowly wth an ice-cold solution of 6-aminopenicillanic acid in aqueous sodium bicarbonate. Throughout the addition of the penicillanic acid the mixture was maintained at 0°C and thereafter allowed to rise to room temperature whilst stirring over a period of 1 hour.

The carbobenzyloxyamino derivative prepared as described above was then shaken with an aqueous suspension of palladium on barium carbonate while passing hydrogen through. After working up in known manner a compound identical with the product of Example 1 (E) was obtained.

EXAMPLE 4

N-trimethylsilyldiethylamine was reacted 6-aminopenicillanic acid fololwing the procedure of U.K. Patent No. 959853 to give 6-N-trimethylsilylaminopenicillanic acid trimethylsilyl ester. This silyl derivative was reacted wth N-carboxyanhydride of 2-aminoindane-2-carboxylic acid prepared accordng to Example 1. A compound identical with the product of Example 1 (E) was obtained.

EXAMPLE 5

Utilising the product prepared according to Example 1(E) the dosage forms described below were obtained following standard procedure.

Formula A

Product of Example 1(E)	275 mg
Calcium carbonate USP*	225 mg
Light liquid petroleum N.F.*	20 mg

Formula B

Compound of Example 1(E)	265 mg
Lactose USP*	15 mg
Stearic acid U.S.P.*	10 mg
Methyl cellulose USP*.400CPS	15 mg

The above amounts of ingredients in each case were encapsulated in individual capsules. Either of the above formulations could be applied for human therapy in combatting infectious disease when administered orally using 4 to 6 capsules per day, depending on the nature and severity of the infection.

*N.F. stands for National Formulary and USP for the United States Pharmacopoeia.

TEST I

A comparison was made of the effectiveness of the product of Example 1(E) against the compound of similar structure which is known as Nafcillin (i.e. the compound 6-(2-ethoxy-1-naphthylcarboxamido) penicillanic acid), details of which are as follows:

Mice were injected intraperitoneally with 0.5 ml of a standardised suspension of one of the infective agents listed below in 5% gastric mucin and randomised. Six hours after infection a single dose of the compound to be tested was given orally. The animals were observed for 14 days and deaths recorded daily. The CD_{50} was determined by the method of Reed and Muench.

The results were as follows:—

Organism	CD_{50}, mg/mouse±S.D.**		Ratio of Activity of Product of Example 1(E)/ Nafcillin
	Product of Example 1(E)	Nafcillin	
Diplococcus pneumoniae (Type I,37)	0.017±0.005	0.143±0.008	8.4
Streptococcus pyogenes (C203)	0.055±0.008	0.335±0.08	9.6
Staphylococcus aureus (Smith)	0.033±0.006	1.06±0.03	32.2
Staphylococcus aureus (CHP)	2.52±0.29	2.65±0.20	1.1

**S.D. Represents the standard deviation.

TEST II

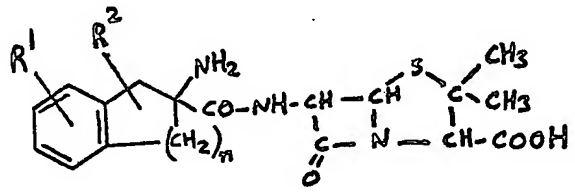
The broad-spectrum anti-bacterial activity of the compound of Example 1(E) are shown by the results given below for the minimum inhibitory concentration of the compound against standard microorganisms. The experiment was carried out as follows:

Stock solutions at 10,000 mg/ml were prepared. Two fold dilutions were made with sterile water. 1 ml. quantities of each dilution were incorporated in 9 ml. seed agar in sterile petri dishes. The hardened surface was innoculated with the test organisms and incubated for 18 hours at 35°C. Results were:—

Test Organism	Minimal Inhibitory Concentration of compound of Example 1(E) in g/ml
Bacillus subtilis 6633	1.95
Staphylococcus aureus 6538P	.976
Staphylococcus aureus Smith	.976
Staphylococcus aureus CHP	7.81
Staphylococcus aureus 53—180	31.3
Neisseria catarrhalis 8193	7.81
Salmonella paratyphi 11737	31.3
Enterobacter aerogenes 884	7.81
Proteus vulgaris 6896	250
Herellea sp. 9955	125
Escherichia coli 6880	250

WHAT WE CLAIM IS:—

1. A compound of the general formula



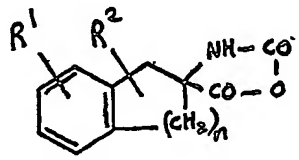
or a salt thereof wherein R^1 and R^2 are the same or different and each is hydrogen, lower alkyl, lower alkoxy, aryl or aryloxy, n is equal to 1 or 2 and the term "lower" means that the radical contains up to 6 carbon atoms.

2. A compound as claimed in Claim 1 wherein R^1 and R^2 are both hydrogen atoms.

3. 6-(Indan-2-amino-2-carboxamido)penicillanic acid.

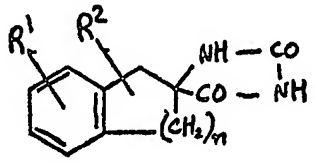
4. The sodium or potassium salts or the hydrochloride, sulphate or fumarate of the compound claimed in Claim 3.

5. A process for the preparation of a compound of the general formula given in Claim 1 which comprises reacting 6-aminopenicillanic acid or a salt thereof with a N-carboxy amino acid anhydride of the following formula



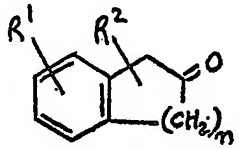
in which R^1, R^2 and n have the values defined in claim 1.

6. A process as claimed in Claim 5 within the N-carboxy anhydride is prepared by reacting a hydantoin of the following general formula



with an alkali metal or alkaline earth metal hydroxide under an inert atmosphere to produce the amino carboxylic acid, followed by reaction with phosgene under anhydrous conditions, the radicals R^1, R^2 and n having the meanings defined in Claim 1.

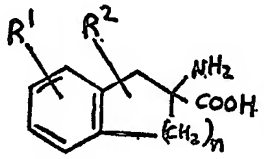
7. A process as claimed in Claim 6 wherein the hydantoin is prepared by heating an indanone or tetralone of the general formula



(in which R^1 and R^2 and n have the meanings defined in Claim 1) with ammonium carbonate and an alkali metal cyanide.

8. A process as claimed in any of claims 5 to 7 wherein 6-aminopenicillanic acid is reacted with N-carboxy-indan-2-amino-2-carboxylic acid anhydride.

9. A process for the preparation of a compound of the general formula given in Claim 1, which comprises coupling 6-aminopenicillanic acid with an acid of the general formula



IV

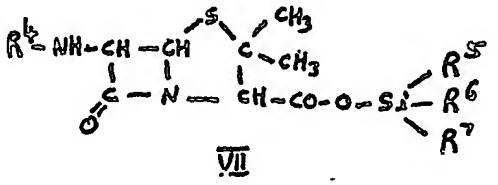
(where R^1, R^2 and n have the meanings defined in Claim 1) in which the amino group is protected, or a salt thereof, and thereafter removing the protecting group under sufficiently mild conditions to avoid destruction of the penicillin nucleus.

10. A process as claimed in Claim 9, wherein 6-aminopenicillanic acid or a salt thereof is reacted with a mixed anhydride prepared by reacting an ester of chlorocarbonic acid with the acid of general formula given in claim 9, or a salt thereof the amino group of said acid or salt being protected.

11. A process as claimed in Claim 9 or claim 10, wherein the amino group is protected by a trityl group or a group of the general formula R^3—OCO, where R^3 is an alkyl, benzyl, substituted benzyl, phenyl or substituted phenyl group.

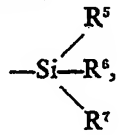
12. A process as claimed in any of claims 9 to 11, wherein the protecting group is removed by hydrogenation.

13. A process for the preparation of a compound of the general formula given in Claim 1, which comprises reacting (a) a silyl derivative of 6-aminopenicillanic acid of the general formula



VII

(where R^4 is a hydrogen atom or the radical



and R^5, R^6 and R^7 are the same or different and each is an alkyl, cycloalkyl, aryl or aralkyl group) or a solution comprising such a silyl derivative, with (b) an acid of the general formula given in Claim 9 or a reactive derivative thereof (in which acid or reactive derivative R^1, R^2 and n have the meanings defined in Claim 1 and in which the amino group is protected), and thereafter removing the silyl group(s) by hydrolysis or alcoholysis.

14. A process as claimed in claim 13, wherein the amino group is protected by reacting the acid in the form of its N-carboxyanhydride.

15. A process as claimed in claim 13 or 14, wherein the reaction of the silyl derivative with the acid or reactive derivative thereof is carried out in the presence of a tertiary amine.

16. A process as claimed in any of claims 9 to 15, wherein R^1 and R^2 are hydrogen and n is equal to 1.

17. A process as claimed in claim 5, substantially as described with reference to Examples 1 or 2.

18. A process as claimed in any of claims 9 to 16, substantially as described with reference to Example 3 or 4.

19. Compounds of the general formula given in Claim 1, when prepared by the process claimed in any of claims 5 to 8, or 17.

20. Compounds of the general formula given in claim 1, when prepared by the process claimed in any of claims 9 to 16, or 18.

21. A pharmaceutical composition comprising a compound as claimed in any of claims 1 to 4 or 19 and a pharmaceutically acceptable carrier.

22. A pharmaceutical composition as claimed in Claim 21 said composition being in the form of a tablet, capsule or solution.

23. A pharmaceutical composition comprising a compound as claimed in claim 20 and a pharmaceutically acceptable carrier.

24. A pharmaceutical composition substantially as described with reference Example 5.

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